PATENT SPECIFICATION

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(19)

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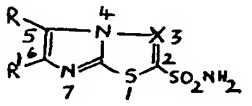
(54) IMIDAZO-THIAZOLE AND -THIADIAZOLE SULPHONAMIDES AND THEIR USE AS THERAPEUTIC AGENTS

(71) We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a class of compounds having cerebral vasodilator activity and is particularly concerned with a novel series of imidazo[2,1-b]thiazole-2-sulfonamides and imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamides. Such compounds are useful for treating conditions attributable to a restriction of blood flow to the brain, including atherosclerosis, occlusion of blood vessels in the brain, stroke and other cerebro-vascular diseases. Particularly useful compounds of the invention are those which have a selective effect on the cerebral vasculature, with a comparatively small effect on blood vessels in other tissues such as peripheral tissue and the kidneys, and so do not cause a serious fall in blood pressure. Many of the compounds of the invention also display marked anti-convulsant activity.

According to the present invention there are provided compounds having the general formula:



(I)

wherein X represents N or CH;

and R and R^1, which may be the same or different, each represent a hydrogen atom; a C_1—C_{10} alkyl group; a C_1 to C_4 alkyl group substituted by an aryl, heteroaryl or C_3—C_{10} cycloalkyl group; a phenyl group; a pyridyl group; a thienyl group; a furyl group; a phenyl, pyridyl, thienyl or furyl group substituted by one or more groups selected from C_1—C_4 alkyl, C_1—C_4 alkoxy, acetoxy, hydroxy, halogen, nitro, amino, C_2—C_5 acylamino, C_1—C_4 alkylsulphonylamino and sulphamoyl; a carbethoxy group; an adamantyl group; or a C_3—C_{10} cycloalkyl group;

or R and R^1 taken together represent an alkylene group of the formula $-(CH_2)_n-$ wherein n is 3, 4 or 5, said alkylene group being optionally substituted by one or more C_1—C_4 alkyl groups;

and the pharmaceutically acceptable acid addition or alkali metal salts of the compounds of the formula (I) which form such salts.

Salts of the compounds of the formula (I) with alkali metal cations are preferably the sodium or potassium salts. Pharmaceutically acceptable acid addition salts of such compounds of the invention as are sufficiently basic include for example the hydrochlorides, hydrobromides, hydroiodides, sulphates, bisulphates, phosphates or acid phosphates, acetates, maleates, fumarates, oxalates, lactates, tartrates, citrates, gluconates, saccharates and *p*-toluene-sulphonates.

When R and/or R^1 is a substituted phenyl, substituted pyridyl, substituted

thienyl or substituted furyl group as defined above, preferably said group contains up to two only of the stated substituents.

The preferred substituted phenyl group is a *p*-hydroxy phenyl group.

In this specification "halogen" denotes fluorine, chlorine, bromine, or iodine.

When R or R^1 is or contains an alkyl group of at least 3 carbon atoms, or contains an alkoxy group of at least 3 carbon atoms, such an alkyl or alkoxy group may be straight- or branched- chain. Preferably, when R or R^1 contains an alkyl group, said group contains 1 to 4 carbon atoms.

The preferred cycloalkyl groups are those containing 5, 6 or 7 carbon atoms.

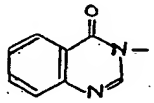
In one aspect of the invention R and R^1 are both other than C_3—C_{10} cycloalkyl.

A preferred group of compounds of the formula (I) are those of the formula (I) wherein:

X represents N or CH;

R represents a hydrogen atom; a C_1—C_4 alkyl group; a phenyl group; or a carbethoxy group;

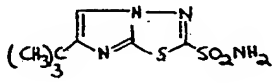
and R^1 represents a hydrogen atom; a C_1—C_4 alkyl group; a C_1—C_4 alkyl group substituted by a group of the formula



an adamantyl group; a phenyl group optionally substituted by up to two groups selected from C_1—C_4 alkyl, C_1—C_4 alkoxy, hydroxy, acetoxy, halogen, nitro, amino, C_2—C_5 acylamino, C_1—C_4 alkylsulphonylamino and sulphamoyl; a pyridyl group; or a thienyl group; or R and R^1 taken together represents $-(CH_2)_4-$.

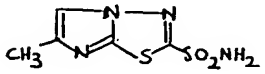
The most preferred compounds of the formula (I) are those in which X is N; R is hydrogen; and R^1 is a phenyl group, a *p*-hydroxyphenyl group, a C_1—C_4 alkyl group or an adamantyl group.

A particularly preferred individual compound is 6-*t*-butyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide of the formula:

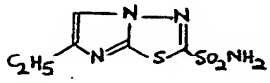


(IA)

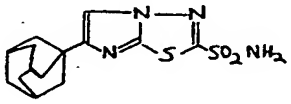
Other preferred individual compounds are the following:



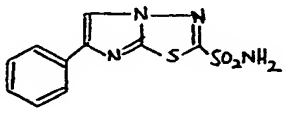
(6-methyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide)



(6-ethyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide)

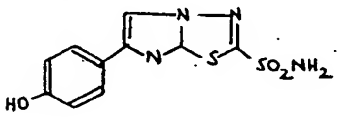


(6-[adamant-1-yl]-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide)



(6-phenyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide)

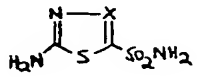
and



(6-*p*-hydroxyphenyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide)

The compounds of the invention may be prepared in a number of ways, including the following:—

(1) The compounds may be prepared by reacting a thiazole-sulfonamide or thiadiazole-sulfonamide of the formula:



(II)

wherein X is as defined for formula (I), with *either* (a) an α-halo carbonyl compound of the formula:

$$R^1.COCH(R)\ (Y) \qquad (III)$$

wherein R and R^1 are as defined for formula (I) and Y is bromine, chlorine or iodine, with the proviso that when R and R^1 are both hydrogen Y is chlorine *or* (b) an acetal of the formula:

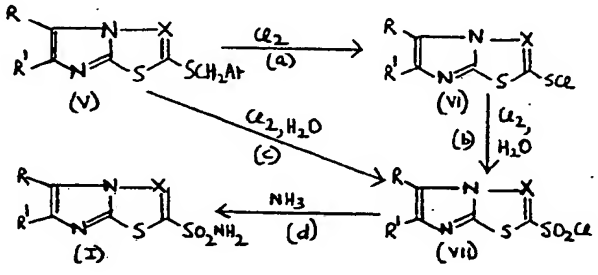
$$R^1.C(OR^2)_2CH(R)\ (Y) \qquad (IV)$$

wherein R and R^1 are as defined for formula (I), R^2 is a C_1—C_4 alkyl group, and Y is bromine, chlorine or iodine, without proviso.

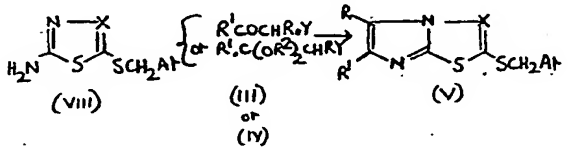
Except when R^1 is hydrogen, it is preferred to use the α-halo carbonyl compound, most preferably the α-bromo carbonyl compound, rather than the acetal. When R^1 is hydrogen, most preferably the dimethyl or diethyl ketal wherein Y is bromine is used.

The reaction is suitably performed by heating the reagents, e.g. at 50° to 100°C, in a reaction-inert organic solvent such as ethanol or dimethylformamide. Long reaction times of up to 3 days are generally necessary. The product may crystallise on cooling. It may however be necessary to partially evaporate the reaction mixture, followed by cooling, before crystallisation will occur. Alternatively, the reaction mixture may be evaporated to dryness to leave the desired product as a residue. The product may be recrystallised, if desired, from a suitable solvent, e.g. methanol, ethanol, acetone or aqueous dimethylformamide, to yield a pure product. The product as isolated may be a free base or may be an acid addition salt formed by reaction of the free base with the hydrogen halide formed as a by-product of the reaction. For example, when R^1 and/or R^2 is a phenyl, thienyl, furyl or pyridyl group (or a substituted derivative thereof) the product as isolated is generally the free base. In other cases, e.g. when R^1 and R^2 are each a hydrogen atom or an alkyl group, the product is generally the hydrogen halide acid addition salt. If necessary, such acid addition salts may be converted to the free base by, for example, reaction with ammonia, sodium carbonate or sodium bicarbonate.

(2) A further preparative reaction as represented by the following sequence of equations is possible, wherein R and R^1 are as defined for formula (I) and Ar represents an unsubstituted or substituted phenyl group, with unsubstituted phenyl preferred:—



Reaction step (a) may be effected by chlorination in a suitable solvent, e.g. carbon tetrachloride, chloroform or benzene. Further reaction with e.g. chlorine in aqueous acetic acid, step (b), produces the sulphonyl chloride. More appropriately, the sulphonyl chloride may be produced directly [step (c)] by oxidative chlorination of the benzylthio compound (V), e.g. with chlorine in aqueous acetic acid. Step (d) may be carried out by reacting the compound of the formula (VII) with aqueous or liquid ammonia. The product will normally be the free base. The starting materials of the formula (V) are either known compounds or may be prepared by methods analogous to those of the prior art. For example, they are generally available via the following route:



The reaction conditions for this route are the same as those for route (1) above, and the product (V) may be isolated in a similar manner.

(3) Salts of the compounds of the formula (I) which are sufficiently basic may be obtained by conventional procedures. Acid addition salts may be formed by the addition of the appropriate acid in a suitable solvent, e.g. methanol or ethanol to a solution of the free base in a suitable solvent, e.g. methanol or ethanol and recovering the product, e.g. by filtration. The product, if desired, may be recrystallised from a suitable solvent, e.g. methanol. It should however be remembered that the product obtained by method (1) above will in certain cases be a hydrohalide addition salt. Alternatively, the alkali metal salts of those compounds of the formula (I) which form such salts are generally available by dissolving the free base in an aqueous or alcoholic solution of the appropriate alkali metal hydroxide and concentrating the resulting solution. The salt may either precipitate from the concentrated solution or it may be left as a residue on evaporation of the solution to dryness. In either case the salt may then optionally be recrystallised from a suitable solvent to produce the pure product.

(4) Some of the compounds of the invention may be prepared from other compounds of the invention by conversion of one type of substituent on the phenyl, pyridyl, thienyl or furyl ring, when present, to another. For example, in the case where it is desired to prepare a compound of the formula (I) having a substituent amino group, the corresponding nitro group may be reduced by catalytic hydrogenation or by other means well-known for such a conversion. Compounds of the invention having a substituent acylamino group may be converted to the corresponding compounds containing an amino group by acid or base hydrolysis, again the techniques being well-known in the art.

The activity of compounds of the invention as cerebral vasodilators is determined by the following methods:—

Based on the theory that vasodilator activity is displayed by a compound which inhibits the enzyme carbonic anhydrase in the brain with consequent elevation of the carbon dioxide level, the compounds of the invention were tested in a procedure similar to that described by F. J. Philpot *et al.*, J. Biochem. 30, 2191 (1936). Mouse brains are removed, blotted and weighed, and then at 0°C chopped into segments and suspended in 5 ml. of 0.25M aqueous sucrose solution. The suspension is then homogenised by 15 strokes in a Potter homogeniser. To 5 ml. of 0.00263 M sodium bicarbonate solution saturated with carbon dioxide at 0°C are added two drops of octan-2-ol, 0.1 ml. of M sucrose and 0.1 ml. of homogenate. This reaction mixture is pre-incubated at 0°C with carbon dioxide continuously bubbling through for 10 minues. Then 20 ml. of bromothymol blue is introduced followed by the rapid addition of 2 ml. of ice-cold 28 mM barbital buffer at pH 7 9 The time taken for the pH to change from 7.9 to 7.0 is recorded and the enzyme rate calculated. A similar experiment not involving addition of the homogenate (no enzyme) is also performed and the time measured as before.

Each test compound is dissolved in a small volume (up to 1 ml.) of N sodium hydroxide solution and the solution is diluted to give a 10^{-3} M solution. Then it is tested at a final concentration in the test medium of 10^{-6} or 10^{-7} M, and the enzyme-catalysed and 'no enzyme' reaction rates are measured. In each case the test compound, enzyme and substrate are pre-incubated for 10 minutes prior to addition of the buffer.

In a second test method, cats are anaesthetised with chloralose (80 mg/kg. i.v.) after induction with halothane, and nitrous oxide/oxygen (3:1 v/v). The animals are allowed to breathe normal room air and the rate and depth of respiration, heart rate and femoral arterial pressure are recorded. An electromagnetic flow probe is placed around the ipsilateral vertebral artery. Zero flow is established by momentarily occluding the artery, in order to calibrate the flow probe. The test compound (dissolved in N/10 sodium hydroxide inisotonic saline with warming and mixing and then back titration to pH 10 with dilute hydrochloric acid) is given at 1 to 10 mg/kg via a femoral vein and readings are taken at intervals for up to 2 hours. Control observations after intravenous administration of the saline vehicle alone, inhalation of 5% CO_2/95° air for 5 minutes, and after 1 mg/kg intravenous injection of papaverine are also made. Blood flow is assessed by measuring the peak (systolic) pulsatile flow and the mean pulsatile flow.

In some experiments 0.5 ml. samples of femoral arterial and internal jugular venous blood are taken at intervals to monitor blood pCO_2, pO_2 and pH using a Radiometer Acid-Base Chart (Type ABC 1).

Results are expressed as percentage change in blood flow and are compared with those of papaverine for potency in increasing flow and for the duration of the effect.

In a third test method a male beagle dog which has previously been trained to lie down quietly for long period (up to 8 hours) is used. The mean arterial vertebral blood flow is monitored using the Doppler ultrasound flow recorder technique, whereby a Doppler 3 mm. diameter flow probe is chronically implanted around the right vertebral artery. The heart rate is also monitored and control base line values are obtained for both parameters.

Papaverine is used as the standard drug and is injected intravenously at 1 mg/kg. Vertebral blood flow and heart rate are monitored continuously until the drug effect subsides. The test compound is administered either intravenously or orally and blood flow and heart rate are similarly monitored. Effectiveness is evaluated by noting the maximum effect produced by the compound, as a percentage increase or decrease in vertebral flow compared to the control readings, and the time at which this occured, and by noting the change in blood flow with time, expressed as the area under the curve of a plot of percentage change against time. The results are compared with those obtained for papaverine.

The effect of compounds of the invention on diuresis and their anti-convulsant activity are determined in mice and dogs by standard methods.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier or diluent selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

For administration to man in the treatment of conditions attributable to the restriction of blood flow to the brain, it is expected that the compounds of the invention would be administered parenterally, e.g. intravenously, in single doses of from 0.1 to 10 mg. per kg. bodyweight per day, or orally in doses of from 0.5 to 25 mg. per kg. in up to 4 divided doses per day. The for average adult patients typical intravenous doses could contain from 10 to 500 mg. of active ingredient, while individual oral doses could be in the form of tablets or capsules containing from 25 to 500 mg. of active ingredient administered up to 4 times a day. The physician will in any event determine the actual dosage most suitable for the individual patient, which will vary with the age, weight and response of that patient.

Thus in one aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I) together with a pharmaceutically acceptable carrier.

In another aspect the invention provides a method of treating an animal having a condition attributable to a restriction of blood flow to the brain, which comprises administering to the animal a compound of the formula (I) or a composition as defined above in an amount sufficient to increase the flow of blood to the brain.

The invention is illustrated by the following Examples in which the preparation of novel compounds according to the invention is described. All temperatures are given in °C.

EXAMPLE 1.

Preparation of imidazo-[2,1-b]-1,3,4-thiadiazole-2-sulphonamide hydrobromide.

A solution of 5-amino-1,3,4-thiadiazole-2-sulphonamide (1.8 g) and bromoacetal (the diethyl acetal of α-bromo-acetaldehyde) (3.0 g) in ethanol (50 ml.) was heated under reflux for 48 hours and then evaporated to a small bulk. Ether was then added until the solution became cloudy and the solution was cooled until crystallisation was complete. The solid was filtered off and crystallised from ethanol to give imidazo [2,1-b]-1,3,4-thiadiazole-2-sulphonamide hydrobromide (0.75 g), m.p. 207—210°.

Analysis:

Found:	C, 17.24;	H, 1.86;	N, 19.93%	
Required for $C_4H_4N_4O_2S_2.HBr$:	C, 16.85;	H, 1.77;	N, 19.65%	

EXAMPLE 2.

Preparation of imidazo-[2,1-b]-thiazole-2-sulfonamide hydrobromide.

By a similar procedure to that described in Example 1, imidazo-[2,1-b]-thiazole-2-sulphonamide hydrobromide, m.p. >300°, was prepared from 2-amino-thiazole-5-sulfonamide and bromoacetal.

Analysis:

Found:	C, 21.45;	H, 2.11;	N, 15.43%	
Required for $C_5H_5N_3O_2S_2.HBr$:	C, 21.14;	H, 2.13;	N, 14.79%	

EXAMPLE 3.

Preparation of 6-methylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide hydrobromide.

A solution of 5-amino-1,3,4-thiadiazole-2-sulfonamide (9.0 g) and bromoacetone (6.9 g) in ethanol (200 ml.) was heated under reflux for 20 hours and then evaporated to a small bulk. Ether was then added until the solution became cloudy and the solution was cooled until crystallisation was complete. The solid was filtered off and recrystallised from ethanol to give 6-methylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide hydrobromide (5.7 g), m.p. 237—239° (d).

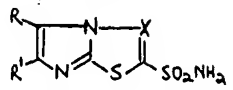
Analysis:

Found:	C, 20.17;	H, 2.37;	N, 18.62%	
Required for $C_5H_6N_4O_2S_2.HBr$:	C, 20.07;	H, 2.36;	N, 18.73%	

EXAMPLES 4 to 11.

By methods similar to that of Example 3, the compounds in the following Table, Table I, were prepared from the appropriate amino-thiazole or -1,3,4-thiadiazole and α-bromo ketone, and were isolated in the form indicated. Both the found and the calculated analyses of the compounds are given, the calculated analyses being in brackets:—

TABLE I



Example No.	R	R¹	X	Form Isolated	M.P. °C	Analysis % (calculated in brackets) C	H	N
4	CH_3	CH_3	N	Hydrobromide salt	235–237° (d)	22.83 (23.01	2.83 2.90	18.16 17.88)
5	H	C_2H_5	N	,, ,,	214° (d)	22.67 (23.01	2.78 2.90	18.08 17.88)
6	CH_3	C_2H_5	N	,, ,,	238–240° (d)	25.77 (25.69	3.39 3.39	17.58 17.12)
7	H	$(CH_3)_3C$	N	,, ,,	278–280° (d)	28.06 (28.15	3.84 3.83	16.58 16.40)
8	H		N	,, ,,	278°	40.05 (40.09	4.62 4.57	12.95 13.36)
9	$-CH_2CH_2CH_2CH_2-$		N	,, ,,	241–242°	28.58 (28.32	3.54 3.27	16.73 16.52)
10	H	CH_3	CH	,, ,,	>255° (slow decomposition)	24.23 (24.17	2.74 2.70	14.18 14.09)
*11	H	$(CH_3)_3C$	CH	Free Base	197–198°	41.15 (41.67	5.03 5.05	15.32 16.20)

* NOTE In Example 11, the compound was purified by thin layer chromatography (silica gel/$CHCl_3$/CH_3OH/0.88 aq.NH_3 20:5:1) and not by recrystallisation from ethanol. As a result of the use of ammonia the product isolated was the free base and not an acid addition salt as in previous Examples.

EXAMPLE 12.

Preparation of 6-phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide.

A solution of 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.8 g) and phenacyl bromide (1.99 g) in ethanol (50 ml.) was heated under reflux for 19 hours. The mixture was cooled, and the resulting solid was filtered off and recrystallised from acetone to give 6-phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide (1.1 g), m.p. 267—269° (d).

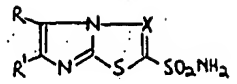
Analysis:

Found: C, 42.95; H, 3.06; N, 20.57%
Calculated for $C_{10}H_8N_4S_2O_2$: C, 42.84; H, 2.88; N, 19.99%

EXAMPLES 13—35.

By methods similar to that of Example 12, the compounds in the following Table, Table II, were prepared from the appropriate amino thiazole or -thiadiazole -sulfonamide and α-bromo ketone, except in Example 14 where the α-bromo-aldehyde was used, and in Example 28 where the α-chloro-ketone was used. The compounds were all isolated as the free bases. Both the found and calculated analyses are given, the calculated analyses being in brackets.

TABLE II



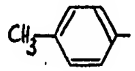
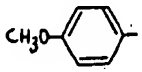
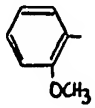
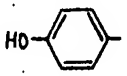
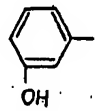
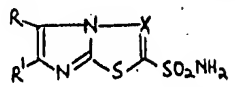
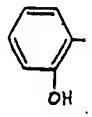
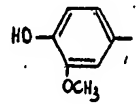
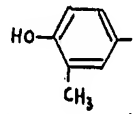
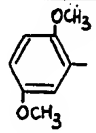
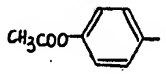
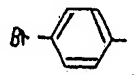
Example No.	R	R¹	X	M.P. °C	Analysis % (Calculated in brackets) C	H	N
13	CH_3	C_6H_5	N	266–268°	45.10 (44.87	3.64 3.42	19.35 19.03)
14	C_6H_5	H	N	230–232°	42.82 (42.84	2.88 2.88	19.66 19.99)
15	$C_2H_5O.CO$	C_6H_5	N	219–220°	44.44 (44.31	3.39 3.43	15.61 15.90)
16	H		N	266–268°	44.81 (44.87	3.42 3.42	18.58 19.03)
17	H		N	269.5–271.5° (d)	42.25 (42.55	3.49 3.25	18.21 18.05)
18	H		N	204–206° (d)	42.77 (42.55	3.28 3.25	18.25 18.05)
19	H		N	283–284° (d)	40.65 (40.53	2.90 2.72	19.18 18.91)
20	H		N	253–255° (d)	40.98 (40.53	2.91 2.72	18.98 18.91)

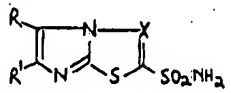
TABLE II (Continued)

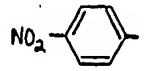
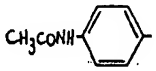
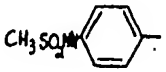
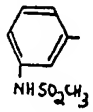
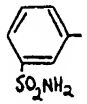


Example No.	R	R¹	X	M.P. °C	Analysis % (calculated in brackets) C	H	N
21	H		N	254–255° (d)	40.53 (40.53	2.67 2.72	18.56 18.91)
22	H		N	290–291°	40.44 (40.48	3.08 3.09	17.28 17.17)
23	H		N	265–267°	42.65 (42.57	3.22 3.25	18.32 18.05)
24	H		N	248–250° (d)	42.30 (42.34	3.53 3.56	16.43 16.46)
25	H		N	262–264° (d)	42.69 (42.59	3.04 2.98	16.23 16.56)
26*	H		N	288.5–290.5° (d)	33.78 (33.44	2.29 1.96	15.59 15.60)

* Reaction carried out in dry dimethylformamide at 100°, and the product obtained by the addition of water to hot solution until crystallisation commenced.

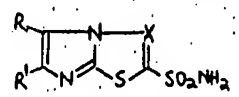
TABLE II (Continued)

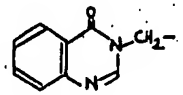
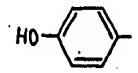


Example No.	R	R^1	X	M.P. °C	Analysis % (Calculated in brackets) C	H	N
27	H		N	310–318° (d)	37.31 (36.92	2.44 2.17	21.66 21.53)
28*	H		N	317–319° (d)	42.70 (42.72	3.34 3.29	20.60 20.76)
29	H		N	277–278° (d)	35.61 (35.38	2.96 2.97	18.47 18.75)
30	H		N	270–272° (d)	35.04 (35.38	3.18 2.97	18.71 18.75)
31	H		N	258–260° (d)	33.01 (33.41	2.51 2.52	19.26 19.48)
32	H		N	284–286° (d)	33.77 (33.55	2.13 2.11	19.23 19.56)

* 72 hour reflux required.

TABLE II (Continued)



Example No.	R	R¹	X	M.P. °C	Analysis % (Calculated in brackets) C	H	N
33	H		N	282–285° (d)	38.10 (38.42	2.38 2.51	24.67 24.90)
34	H		N	271° (d)	42.66 (43.08	2.64 2.78	23.21 23.2)
35	H		CH	286° (d)	44.37 (44.73	3.07 3.07	13.65 14.23)

EXAMPLE 36.

Preparation of 6 - (4 - Amino phenyl)imidazo[2,1 - b] - 1,3,4 - thiadiazole - 2-sulphonamide.

A mixture of 6-(4-acetylamino)phenylimidazo-[2,1-b]-1,3,4-thiadiazole-2-sulphonamide (0.5 g) and 10% hydrochloric acid (7 ml.) was heated under reflux for 1 hour. The resulting clear solution was cooled and basified by the addition of of solid sodium carbonate. The resulting solid was filtered off, washed with water and recrystallised from aqueous dimethylformamide to give 6-(4-amino phenyl)imidazo[2,1-b]-1,3,4-thiadiazole-2-sulphonamide (0.25 g), m.p. >350°.

Analysis:

Found: C, 40.68; H, 3.06; N, 23.41%

Required for $C_{10}H_9N_5O_2S_2$: C, 40.67; H, 3.07; N, 23.72%

The following Example illustrates a typical pharmaceutical composition containing a compound of the formula (I):

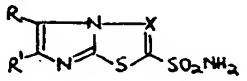
EXAMPLE 37.
Parenteral Formulation

	mg/ml
Active ingredient (product of Example 7)	7.5
Sodium chloride	7.9
Sodium hydroxide (sufficient in pH adjustment)	
Water (sufficient to make up volume)	

The active ingredient and sodium chloride are dissolved in sterile, pyrogen-free and carbon dioxide-free water under nitrogen, the pH is adjusted to 11.75 with 10% by weight aqueous sodium hydroxide and the volume made up with similar water. The solution is then filled into 5 or 10 ml. ampoules through a filter and autoclaved at 115°C for 30 minutes.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



(I)

wherein X represents N or CH;

and R and R^1, which may be the same or different, each represent a hydrogen atom; a C_1—C_{10} alkyl group; a C_1 to C_4 alkyl group substituted by an aryl, heteroaryl or C_3—C_{10} cycloalkyl group; a phenyl group; a pyridyl group; a thienyl group; a furyl group; a phenyl, pyridyl, thienyl or furyl group substituted by one or more groups selected from C_1—C_4 alkyl, C_1—C_4 alkoxy, acetoxy, hydroxy, halogen, nitro, amino, C_2—C_5 acylamino, C_1—C_4 alkylsulphonylamino and sulphamoyl; a carbethoxy group; an adamantyl group; or a C_3—C_{10} cycloalkyl group;

or R and R^1 taken together represent an alkylene group of the formula $-(CH_2)_n-$ wherein n is 3, 4 or 5, said alkylene group being optionally substituted by one or more C_1—C_4 alkyl groups;

and the pharmaceutically acceptable acid addition or alkali metal salts of the compounds of the formula (I) which form such salts.

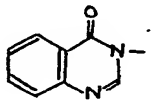
2. A compound as claimed in claim 1 wherein R and R^1 are both other than C_3—C_{10} cycloalkyl.

3. A compound as claimed in claim 2 wherein

X represents N or CH;

R represents a hydrogen atom; a C_1—C_4 alkyl group; a phenyl group; or a carbethoxy group;

and R^1 represents a hydrogen atom; a C_1—C_4 alkyl group; a C_1—C_4 alkyl group substituted by a group of the formula:



an adamantyl group; a phenyl group optionally substituted by up to two groups selected from C_1—C_4 alkyl, C_1—C_4 alkoxy, hydroxy, acetoxy, halogen, nitro, amino, C_2—C_5 acylamino, C_1—C_4 alkylsulphonylamino and sulphamoyl; a pyridyl group; or a thienyl group,

or R and R^1 taken together represents $-(CH_2)_4-$.

4. A compound as claimed in claim 3 wherein X is N, R is a hydrogen atom, and R^1 is a phenyl, *p*-hydroxyphenyl, C_1—C_4 alkyl or adamantyl group.

5. 6-*t*-Butyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide.

6. 6-Methyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide.

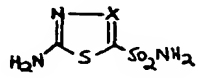
7. 6-Ethyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide.

8. 6-(Adamant-1-yl)-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide.

9. 6-Phenyl-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide.

10. 6-(*p*-Hydroxyphenyl)-imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide.

11. A process for preparing a compound of the formula (I) as defined in claim 1, which comprises reacting a sulfonamide of the formula:



(II)

wherein X is as defined in claim 1, *with either:*
(a) an *α*-halo-carbonyl compound of the formula:

$$R^1.COCHR.Y \qquad (III)$$

wherein R and R^1 are as defined in claim 1 and Y is bromine, chlorine or iodine, with the proviso that when R and R^1 are both hydrogen Y is chlorine, *or (b)* an acetal of the formula:

$$R^1.C(OR^2)_2.CH(R)(Y) \qquad (IV)$$

wherein R and R^1 are as defined in claim 1, R^2 is a C_1—C_4 alkyl group and Y is chlorine, bromine or iodine.

12. A process as claimed in claim 11 wherein the sulfonamide of the formula (II) is reacted with an *α*-halo-carbonyl compound of the formula (III) in which R^1 is as defined in claim 1 except hydrogen and Y is bromine.

13. A process as claimed in claim 11 wherein the sulfonamide of the formula (II) is reacted with an acetal of the formula (IV) wherein R^1 is hydrogen, R^2 is methyl or ethyl and Y is bromine.

14. A process as claimed in claim 11 substantially as hereinbefore described in any one of Examples 1 to 36.

15. A compound of the formula (I) as defined in claim 1 which has been prepared by a process as claimed in any one of claims 11 to 14.

16. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 and 15 together with a pharmaceutically acceptable carrier.

17. A method of treating a non-human animal having a condition attributable to a restriction of blood flow to the brain, which comprises administering to the animal a compound as claimed in any one of claims 1 to 10 and 15 or a composition as claimed in claim 16 in an amount sufficient to increase the flow of blood to the brain.

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Agent for the Applicants.

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